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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,046	02/04/2000	Sabine Neirynck	VIB-08	8244

7590 12/18/2001

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	9

DATE MAILED: 12/18/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,046	NEIRYNCK ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *26-51* is/are pending in the application.

4a) Of the above claim(s) *42-45 and 47-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-41, 46* is/are rejected.

7)☒ Claim(s) *27,28 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Europe on August 5, 1997. It is noted, however, that applicant has not filed a certified copy of EP 97202434.3 application as required by 35 U.S.C. 119(b).

Election/Restrictions

Claims 42-45 and 47-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group II, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claim Objections

Claims 27 and 28 are objected to because of the following informalities: there is inconsistency between which portion of "poly" and "peptide" applicant wishes to put into parenthesis. It would be acceptable if applicant wishes to delete all parentheses, since a parenthesis is not required for this word. However, appropriate correction is required to correct the inconsistency.

Claim 46 is objected to because it depends from claim 44, which is withdrawn from consideration directed to the non-elected group.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-41 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is vague and indefinite because the metes and bounds for what would comprise a functional fragment of an extracellular part of an M2 protein that comparably elicits immunoprotection has not been defined. The functional fragment is also indefinite because it cannot be determined from the passive language, "capable", whether or not the fragment actually elicits an immunoprotective response. Applicant cannot refer to a Table of sequences in the claims. Applicant is required to insert SEQ ID NOs to clearly define which amino acid sequences are encompassed in the claim. The claim also recites that a "similar" integral membrane protein of influenza B or C virus is used. Applicant has not defined what is meant by similarities since influenza B and C strains do not have an M2 protein, see the last paragraph of the first column on page 1400 of Fields et al. (Virology, 3rd edition 1996. Philadelphia; Lippencott, Williams, and Wilkins.) Do the integral proteins share functional, structural, sequence, or other similarities or homologies? It also cannot be discerned what is intended by "statistically significant immuunoprotection". What criteria are used by applicant to determine the "statistical significance" of immunoprotection? This phrase is vague and indefinite because the criteria defining "statistically significant" to one may not be shared by another. In addition, if a component possesses immunoprotective properties against a pathogen, how would one determine whether one component was more immonoprotective compared with another component since both components would have protective capabilities? The claim also refers to an undefined "immunoprotective dose". The claim is also vague and indefinite for reciting,

"modified versions" of an extracellular part of an M2 protein that react with polyclonal antisera since polyclonal antisera are not particularly immunospecific. Polyclonal antibodies used to bind to the modified versions would also recognize other unrelated peptides, fragments, and epitopes. This rejection affects all dependent claims.

Claim 28 lists C3d domains are the presenting peptide. Cruse et al. (Illustrated Dictionary of Immunlogy. 1995. CRC Press, Boca Raton.) defines C3d as a 33-kD B cell growth factor. Which "domain" of C3d is applicant referring to? Claim 28 is also indefinite because it recites an improper Markush group. The applicant is referred to MPEP 2173.05(h) and advised to reformat the claim to read "wherein R is a material selected from the group consisting of A, B, C **and** D" or "wherein R is A, B, C **or** D".

Claim 30 refers to "peptide memetics". It is presumed that this component mimics a peptide in some respect, but the nature of the mimicry is not defined. There appears to be claim inconsistency between a component that mimics a peptide in claim 30 and a peptide mimic that is non-peptidic in structure from claim 29, see the definition of peptide in Dorland's Illustrated dictionary. 1994, 28th edition. Philadelphia; WB Sauders Company, page 1254.

The "additional domain" of claim 31 is vague and indefinite. What kind of domain and where is it derived from?

Claim 33 states that the presenting carrier does not "substantially alter" the tertiary structure of the fusion partner. The degree of what is considered to be substantially altered has not been defined.

Claim 38 is confusing it cannot be determined if applicant is referring to the membrane fragment of an influenza virus since M2 is an influenza virus membrane protein of the virus or if

the claim is referring to the membrane of the acceptor cell in claim 37. If applicant is referring to the acceptor cell membrane, claim 38 conflicts with claim 37 because an acceptor cell membrane that the fusion protein is anchored to would not comprise membrane fragments, but an intact membrane. It is accepted terminology in the art that virions comprise envelopes and cells comprise membranes.

Claim 39 states that the fusion product is expressed in or on a cell "envelope". It is presumed applicant intends for the fusion product to be expressed on a cell membrane since cells do not have envelopes.

Regarding claim 40, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 46 is drafted in the product-by-process format. The recitation of a process imitation in claim 46 is not viewed as positively limiting the claimed product. An adequate description of how the processes make the claimed influenza antigen unique to other influenza antigens is absent and fails to show that the process of making recited in claim 46 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an influenza antigen comprising a functional fragment of an influenza M2 protein that elicits statistically higher immunoprotection compared with test subjects not receiving other M2 fragments. The specification only uses the N-terminal portion of the M2 protein. The specification does not teach other possible functional fragments of M2 or the immunoprotection of the possible fragments. The specification also does not teach what would be considered a similar M2 integral membrane protein from influenza virus B or C since these viruses do not contain M2, see the citation of Fields et al. above. Therefore, the only functional fragment that the disclosure has adequately described and is in possession of is the N-terminal fragment of M2 of influenza virus A comprising amino acids 2-24.

The claims are also directed to modified versions of the extracellular portion of the M2 protein that still reacts with polyclonal antisera. Although the specification modifies two leucine codons for the expression of the M2 protein in *L. lactis* cells on pages 48-49 and identifies up to three amino acid differences between the N-terminus of the A/Fort Monmouth/1/47 (H1N1) strain and other influenza virus strains, it is determined that the specification does not possess all possible amino acid sequence derivatives of the M2 protein that could react with polyclonal antiserum since polyclonal antibodies are not immunospecific. See the teachings of Estabrook et al. (J Invest Surg 1989; 2 (3): 211-22, abstract only) for a general teaching in the art regarding monoclonal antibody specificity. Since the genus embraces a wide variety of possible derivatives and variants of each polypeptide or protein, the single species of each polypeptide or protein is not seen as representative for the full genus claimed.

The specification also does not describe or how one would obtain every possible domain from any source that would enhance cellular immunogenicity of a the claimed influenza antigen. The specification also does not describe how the skilled artisan could immediately identify every influenza-specific T helper or cytotoxic T cell epitope.

Claim 33 states that the presenting carrier does not alter the tertiary structure of the fusion partner (i), the extracellular portion of M2. When the N-terminal portion of M2 is expressed as a fusion protein, the natural tertiary structure has already been altered. In addition, the specification does not examine the tertiary structure of the M2 protein fragment to determine whether the tertiary structure of the protein has been altered. The specification only teaches that the an M2 epitope is expressed on the outside of the hepatitis B core antigen on page 41, lines 14-17. There is no data presented by x-ray crystallography or any other conventional means (see Gray et al. Protein Science. 1998; 7 (11): 2359-73, abstract only) in the specification that would indicate possession of an unaltered tertiary structure of the M2 fragment.

Claims 26-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an influenza antigen comprising a fusion protein comprising the extracellular portion of the influenza M2 protein, or fragment thereof, and a presenting carrier that protects against all influenza virus strains. As discussed above, the specification only uses the N-terminal portion of the M2 protein from one influenza virus strain. The specification does not teach other possible functional fragments of M2 or would be considered a similar M2

integral membrane protein from influenza virus B or C since these viruses do not contain M2, see the citation of Fields et al. above.

The skilled artisan would not be able to predict which extracellular fragments of M2 would be immunoprotective without undue experimentation because the specification has only described a single species. The skilled artisan would doubt that the claimed fusion protein would be able to prevent and treat any influenza virus infection. The working examples fail to demonstrate that the mice were protected against every type of influenza virus and the disclosure fails to teach how one skilled in the art could anticipate all of the possible mutations that can occur in any influenza virus. Fields et al. teaches that influenza viruses undergo antigenic shift and antigenic drift, which affects HA and N proteins, see the last paragraph on page 1417. Since the instant vaccine composition is primarily composed of M2 and the working examples are limited to administering only one type of influenza virus at challenge, the specification is not reasonably enabled for protection against every possible strain of influenza. The specification teaches that the M2 protein of influenza virus is conserved and lists sequences of several virus types in Table 1. However, the skilled artisan would not doubt that this protein would confer protection against any strain of influenza or influenza virus A strain because Zebedee et al. (Journal of Virology. 1988; 62 (8): 2762-2772) teaches that the N-terminus of the M2 protein is not conserved among all strains, especially in residues 11 and 14, which interferes with antibody binding due to a conformational change of the protein. See figure 4 and the second column on page 2766, and the paragraph bridging columns 1 and 2 on page 2770. Zebedee et al. also teaches that M2-specific monoclonal antibodies against the M2 protein could not prevent initial viral infection, but only restricts growth of some influenza virus strains, see the section bridging

the bottom of page 2767 to the page 2769, and page 2771. Slepushkin et al. (Vaccine. 1995; 13 (15): 1399-1402, also teaches that vaccination with M2 shortened the duration of virus shedding in mice, but also teaches that preliminary results indicate that the immune response in humans with the M2 protein after infection would be "of lower activity and/or less durable", see the last paragraph.

Data from the working examples are inconclusive with respect to the protective nature of the antigen. On page 42, different groups of mice were administered a vaccine (IM2HBcm) containing the N–terminal portion of the M2 protein and the hepatitis core protein. Although the specification teaches that the mice were protected by subsequent challenge, page 55 of the specification teaches that these mice also demonstrated high morbidity. The working examples also demonstrate inconsistency with regard to the protective effect of the instant antigen. On pages 53, 54, and figure 32, the experimental data shows that all of the mice that were passively immunized with IM2HBcm antisera were protected against viral challenge, but the mice that only received IM2Hbcm antigen died at the same rate as the negative control group. The protection observed in one experiment and lack of protection in another experiment with the same M2 extracellular region demonstrates unpredictability. Furthermore, the skilled artisan would not conclude that passive immunization with the instant antigen would result in protection because it is known that passive immunization is brief in the host, see page 229 of Cruse et al. In addition, the specification on page 5 teaches that passive immunization is not effective in humans.

Therefore, due to the broad scope of the claims that is directed to treating and preventing any type of influenza virus infection, the unpredictable nature in the art with regard to vaccine

development, the unpredictable nature of influenza viruses with regard to antigenic drift and shift, the lack of ability for the skilled artisan to make any immunoprotective fragment of the influenza M2 protein, the lack of direction provided by the inventor as to how to make or immediately identify other fragments or modified versions of the N-terminal M2 protein that are immunoprotective, the discrepancy in the working examples between whether the recombinant antigens really are protective or whether only passive immunization works, the state of the art for the lack of protection developed from passive immunity in humans, the lack of working examples demonstrating that the instant antigen is protective against all types of influenza virus infection, and the state of the art indicating that the M2 protein does not prevent initial infection, but only restricts growth in a few strains, it is determined that an undue amount of experimentation would be required of the skilled artisan to make and use the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 46 is rejected under 35 U.S.C. 102(b) as being anticipated by Melnick et al.

The claim is drawn to an influenza antigen made by a method. Melnick et al. teaches a method for purifying an influenza HA antigen, see claims 1 and 5 and column 11. The antigen of Melnick et al. would be indistinguishable from the instant influenza antigen of claim 46, even though the methods of making the antigens are distinct.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
December 7, 2001

James C. Housel
JAMES HOUSEL 12/17/01
SUPERVISORY PATENT EXAMINER
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